

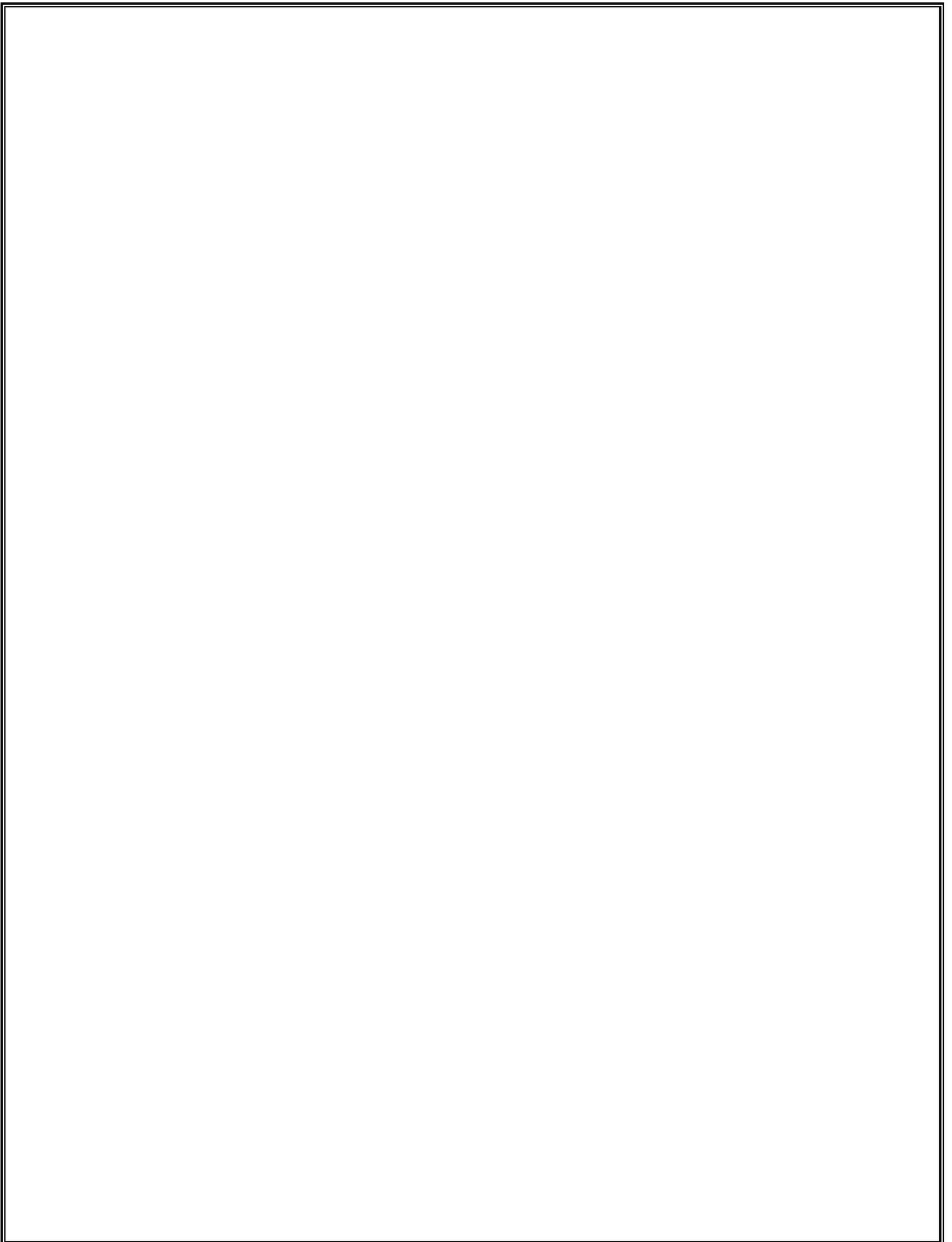
DTT Project



Annual Report



Compiled by the TB Program Evaluation & Research Unit, University of Alberta





DTT PROJECT

Annual Report

DTT Project Annual Report
Year 2: 2007-08
Compiled by TB PE&RU, University of Alberta



UNIVERSITY OF
ALBERTA



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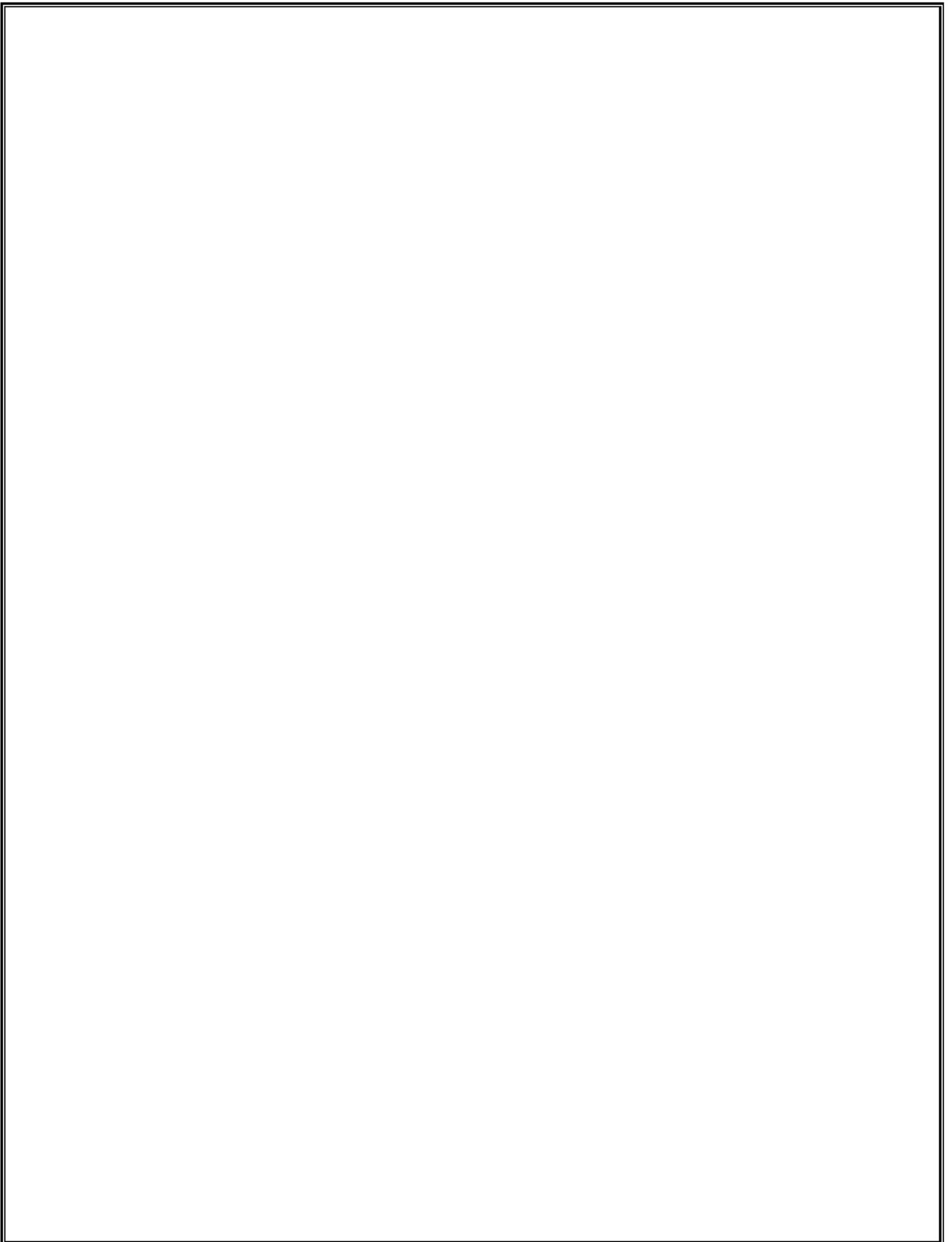


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1. Introduction

The CIHR/Health Canada-funded Determinants of TB Transmission (DTT) Project has recently completed its second of five years. In person data collection of eligible cases (Canadian-born, adult [>14 years], culture positive, respiratory cases of TB in the Prairie Provinces) is ongoing and has been the primary focus for the year. While registry and genotype data gathering will continue for the remainder of the fingerprint window ending December 31, 2010, in person data collection will wrap up in early 2009.

In the last year the study team welcomed a new data manager to the project, development of trainees became a larger priority, ethics approvals were updated, Network Committees provided feedback and support to the team, study coordinators continued to invoke awareness of and support for the project, and recruitment estimates are on track. Preliminary findings are now available for Objective 1 of the project, and qualitative meetings have helped to develop further lines of inquiry for Objective 2 (See text box below for project objectives). Descriptive and recruitment statistics for Objective 2 are reported herein.

DTT Project Objectives

Objective 1:

To characterize the occurrence and spread of particularly virulent strains of TB in order to understand the potential role of clinical and environmental determinants of TB transmission through the retrospective analysis of all culture-positive TB cases in Alberta from 1990-2007

Objective 2:

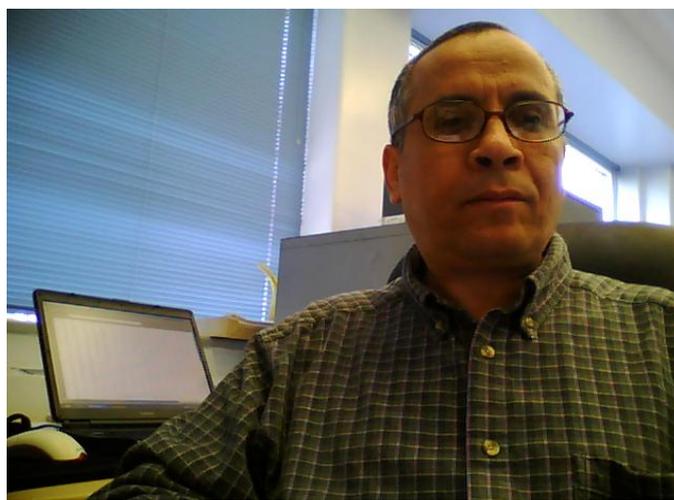
To prospectively identify determinants of TB transmission on the prairies, with emphasis on Aboriginal people, through the use of structured and semi-structured interviews and DNA fingerprinting of TB case isolates to capture all transmission events leading to early disease

2. Study Team

The study team, consisting of eight investigators, four full time research staff, and numerous collaborators, continues to coalesce and is more dedicated than ever. Highlights from the last year include an in-person meeting of the study team and the addition of a new Data Manager. Furthermore, after assisting with training and providing invaluable qualitative input to the project, Dr. Maria Mayan of the International Institute for Qualitative Methodology in Edmonton was officially added as a co-investigator to the CIHR grant in August.

New Data Manager

In October 2007 the team welcomed Halim Elamy to the project. With a background in Computing Science and Statistics, Halim quickly rose to the task of developing a complex database to securely and accurately store and analyse the many elements of data collected for the project. The new database, now in the advanced testing stage, will be rolled out to Saskatchewan and Manitoba in July 2008.



Data Manager, Halim Elamy, joined the DTT project in October 2007

Co-Investigator Meeting

In January 2008 the co-investigators and research staff met in Edmonton for the first face to face meeting of the entire study team. The group discussed database development, project targets, future planning, and the finalization of the project's Terms of Agreement. The meeting helped to solidify the team and affirmed to those involved the mutual goal of TB elimination in the Prairie Provinces.

3. Training

Training of both research staff and trainees is an important aspect of the DTT project. With research staff now up-to-date on training, trainees were a priority in 2007-08.

PhD Training

In 2007-08 PhD student Deanne Langlois-Klassen continued her analysis of the Beijing/W family of strains in Alberta. In December 2007, Deanne was awarded a Myer Horowitz Graduate Scholarship for her efforts. She presented a poster of preliminary findings at the International Union Against TB and Lung Disease (IUATLD) Conference in San Diego in March 2008 and was invited to present a poster at the Alberta Provincial Laboratory for Public Health's Scientific Symposium in Edmonton in May 2008.

Summer Student

In the winter of 2008, a successful application was submitted to Canada Summer Jobs to provide partnership funding for a summer student to assist with the cleaning and maintenance of the Beijing/W database. A competition was held in the spring, and a summer student was identified for summer 2008.

Future Trainees

With the wealth of data and expertise on the project, investigators on the DTT project are hoping to recruit additional trainees for 2009. Currently we are advertising for a post-doctoral position in Epidemiology and are on the look out for additional graduate students to take up different aspects of the research and/or related projects.

Defining the Clinical and Epidemiological Characteristics of Beijing/W Strains of *Mycobacterium tuberculosis* in a Major Immigrant-Receiving Province of Canada

Langlois-Klassen D, Kunimoto D, Saunders D, Chui L, Boffa J, Long R
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Background

Beijing/W Family of Strains

- Tuberculosis disease (TB) resulting from the Beijing/W family of *M. tuberculosis* strains is a potentially important public health issue in many low incidence countries¹
- The spread of Beijing/W strains raises significant concerns due to its association with:
 - TB outbreaks;^{2,3}
 - Anti-tuberculosis drug resistance;^{4,5}
 - In laboratory studies, bacille Calmette-Guérin (BCG) vaccination provides poorer protection against Beijing/W strains than against other strains⁶
- Beijing/W strains account for 77% of all *M. tuberculosis* strains in the Beijing/W "hotspot" countries of China, Hong Kong, Vietnam and Korea^{7,8}
- Globaly, 91% of all *M. tuberculosis* strains are Beijing/W⁹

Canada's Interest in the Beijing/W Phenomena

- 20% of the 200,000-250,000 new immigrants arriving annually are from the Beijing/W "hotspot" countries¹⁰
- A preliminary study using Beijing/W reference strains identified by IS6110-RELP¹¹ impregnating noted Beijing/W in significant numbers of Canadian-born Aboriginal (Aboriginal) and foreign-born Asian-Pacific persons (Long unpublished)

Beijing/W Family Strains in Alberta by Ethnic Group (1994 - 1998)

Methods

Study Population

- The study population consists of culture-positive cases of *M. tuberculosis* in Alberta from January 1990 to July 2007

Time Period (years)	Canadian-born	Canadian-born Aboriginal	Foreign-born	Total
1990-1994	126	37	80	243
1995-1999	172	19	78	269
2000-2004	75	22	48	145
2005-2007	28	13	21	62
Total	301	91	227	619

Note: It is recognized that the ratios may not be consistent to 20% of all culture-positive cases.

Data Sources

- DNA fingerprinting of all *M. tuberculosis* isolates in the database was completed using IS6110 restriction fragment length polymorphism (RFLP). Spotting was used for the secondary typing of isolates with less than six copies of IS6110
- Beijing/W typing was performed by PCR-based region-of-difference analysis (deletion of RD105)¹² on a randomly selected sample of *M. tuberculosis* isolates from 1990 to 2005
- The remaining isolates from 1990 to 2005, as well as culture-positive *M. tuberculosis* cases up to July 2007, will be Beijing/W typed in 2008
- Demographic, clinical and other patient-level data was extracted from Alberta Health and Wellness' TB Registry
- The socio-economic status of TB patients will be approximated from Statistics Canada and Indian and Northern Affairs Canada data

Analyses

- Comparisons of Beijing/W and non-Beijing/W cases for characteristics such as: age at diagnosis, gender, ethnic group, disease site, human immunodeficiency virus (HIV) status, sputum smear positivity, and first-line anti-tuberculosis drug resistance using Chi-square tests (or Fisher's Exact test when $n \leq 25\%$ of cells had an expected cell count less than 5) were completed
- Odds ratio and 95% confidence intervals were calculated for Beijing/W status in foreign-born persons compared to Canadian-born persons; foreign-born persons from the Western Pacific region compared to foreign-born persons from other regions; and Aboriginal persons compared to Canadian-born non-Aboriginal persons
- The frequency and proportion of Beijing/W strains in foreign-born persons and Canadian-born persons was graphed over 5-year periods (i.e., 1990-1994, 1995-1999, 2000-2004) to assist in visualizing possible Beijing/W trends

Conclusion

- There is remarkable consistency between the patterns of Beijing/W in Alberta's foreign-born persons and global Beijing/W patterns
- Preliminary data suggests that Canadian-born Aboriginal persons are not disproportionately affected by Beijing/W strains compared to Canadian-born non-Aboriginal persons
- Thus, as said compared to non-Beijing/W strains, *M. tuberculosis* Beijing/W family strains in the Canadian-born population do not appear to be hyperendemic nor associated with higher rates of first-line drug resistance
- In foreign-born persons, Beijing/W strains are significantly more likely to be associated with first-line anti-tuberculosis drug resistance than non-Beijing/W strains

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Results

Of the 954 *M. tuberculosis* isolates from 1990 to 2005 that have been genotyped, 274 (28.7%) were of Beijing/W lineage

Year	Canadian-born	Canadian-born Aboriginal	Foreign-born	Total
1990-1994	126	37	80	243
1995-1999	172	19	78	269
2000-2004	75	22	48	145
2005-2007	28	13	21	62
Total	301	91	227	619

Prevalence of Beijing/W Family Strains in Foreign-Born Persons

Prevalence of Beijing/W Family Strains in Canadian-Born Persons

- Beijing/W strains were significantly ($p < 0.001$) more likely to be found amongst foreign-born persons than Canadian-born persons (OR 4.517, 95% CI 3.110 to 6.855)
- Foreign-born persons originating from the Western Pacific region, which includes the Beijing/W "hotspot" countries, were significantly ($p < 0.001$) more likely to be associated with Beijing/W family strains than persons from other regions (OR 8.216, 95% CI 5.426 to 12.448)
- The penetration of Beijing/W strains into Aboriginal and non-Aboriginal persons was similar ($p = 0.475$; OR 0.767, 95% CI 0.368 to 1.600)

Funding

First Nations and Inuit Health, Health Canada

Department of Medicine; TB Program Evaluation and Research Unit; and
Department of Public Health Sciences

Poster presented by Deanne Langlois-Klassen, PhD candidate, at the IUATLD North American Family Region Conference in San Diego in March 2008.

4. Ethics Approvals

In the first year of the project, the groundwork was completed for the submission to the respective Ethics Boards in each province. In 2007-08, study coordinators have submitted updates to their respective provincial health bodies, university Ethics Boards, Regional Health Authorities, hospitals, and institutions. The following outlines each provinces individual ethics submissions, and approvals:

Manitoba:

In Manitoba an annual report was submitted to the University of Manitoba Research Ethics Board in September of 2007. Approval was granted for the continuation of the study. Regular updates have been submitted and approvals received when study instruments have been modified or processes altered. Annual updates were submitted to the Health Sciences Centre, St. Boniface Hospital, and Burntwood Regional Health Authority. In September of 2007 a meeting with the study Investigators and Manitoba Health HIPC committee established an agreement in principle for the extraction of data from the TB Registry. Negotiations are ongoing regarding the details of the agreement.

Saskatchewan:

An annual update was submitted and approval received from the University of Saskatchewan in Decemeber 2007. Official approval was also received from the Regina/Qu'Appelle Health Region.

Alberta:

An annual update was submitted and renewed approval received from the University of Alberta in September and Health Canada in November 2007.

5. Provincial Network Committees

The role of the Provincial Network Committees in the DTT project is important to reiterate in this 2nd Annual Report. The Committee's role, although less in the data-gathering period of the study, is essential in ensuring that the study continues to honour the principles of consultation with the community in which it is conducting its study. As stated in the first annual report, the role of the Network Committees is to ensure ongoing feedback and appropriate conduct throughout the study.

In spring and summer of 2007, study coordinators provided updates to members. In late November, all three provinces held face to face meetings with their respective Network Committees. Recruitment numbers, descriptive statistics, and preliminary data were reported to Committee members and discussion ensued, resulting in minor modifications to the qualitative interview guide and generating ideas for dissemination of data in the latter stages of the project. These meetings also provided an opportunity to bring forward any concerns that study coordinators may have encountered.

Specific topics that came up included discussion on participant recruitment within communities. It was noted that the process for recruitment differs between provinces due to the distinct protocols for treatment and follow-up of tuberculosis. In Manitoba the committee members were interested in knowing more about how the information gathered during the study would be disseminated to the communities. Committee members raised the hope that the results of this study would highlight the burden of illness that is borne by the Aboriginal community. Discussions in Saskatchewan revolved around the effect of undertaking interviews in the community instead of in hospital, and how that could produce interesting differences in how the disease is perceived and what issues are important to those affected by the disease as well as the larger community. In Alberta the Network Committee discussed the need for more information regarding the disease. The Committee members voiced their hope that one of the results of the study would be increased education and awareness at the community level.

6. Study Awareness

Study awareness is important to ensure that community stakeholders and associated health staff are conscious and supportive of the project. Although the focus of the last year was heavily weighted on data collection, study awareness activities and relationship building continued throughout the year. Highlights from each province are outlined below.

Manitoba:

In May 2007, the Manitoba study coordinator presented on the project at a TB Conference in the Pas. The presentation helped to garner support for the project in both the province and the community, and Chief and Council followed up with a letter of support.

Saskatchewan:

In December 2007, a project summary and update were provided to the Saskatchewan TB Advisory Group in Saskatoon. The report was well received, and several questions were posed on the different facets of the project, particularly on DNA fingerprinting. Dr. Ibrahim Kahn of First Nations & Inuit Health invited the Saskatchewan study coordinator to attend future meetings for updates on the descriptive statistics and events.

Alberta:

In January 2008, nurses at the Calgary TB Clinic were updated on the project, and in March, study coordinators presented a research update on the project at the 6th TB Conference in Edmonton.



Study Coordinators (left to right) Kathleen McMullin, Jody Boffa, and Carmen Lopez-Hille prepare to present at the 6th Tuberculosis Conference in Edmonton in March.

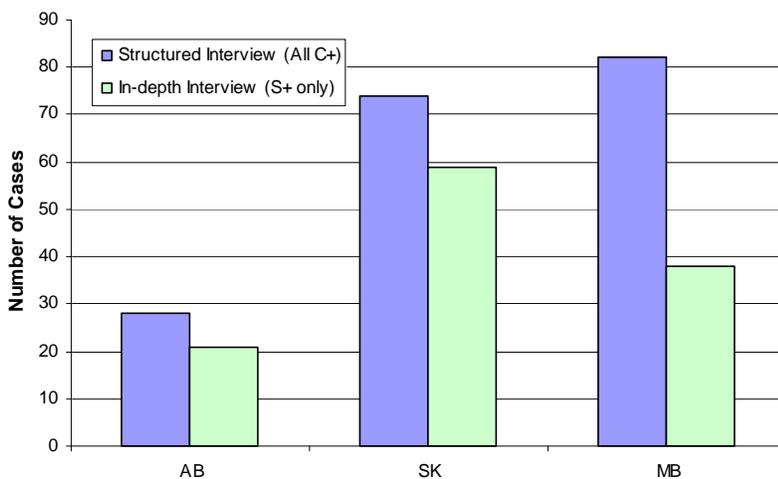
7. Data Collection

Year 2 of the project focussed primarily on data collection in the Prairie Provinces. Study coordinators undertook structured interviews with Canadian-born, culture positive, adult (>14 years), respiratory cases of TB and in-depth interviews with cases that were also smear positive for acid-fast bacilli. In Saskatchewan, where mobile clinics extend to remote areas of the province, study coordinator Kathleen McMullin met with participants in a number of communities. In Alberta and Manitoba, many participants were interviewed in hospitals in Edmonton and Winnipeg, respectively, with data collection extending to external cities and communities for participants treated at remote sites.

Recruitment

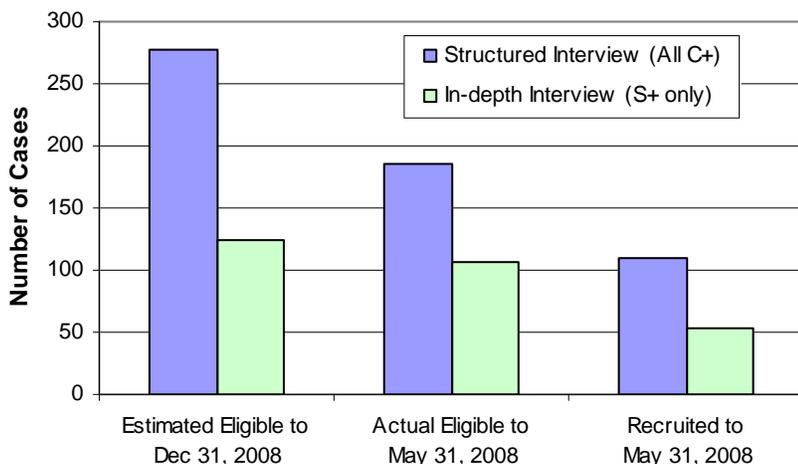
As of May 31, 2008, 109 participants had been recruited to undergo the structured interview: 24 in Alberta, 41 in Saskatchewan, and 44 in Manitoba. Of these, 54 have undertaken the in-depth interview: 16 in Alberta, 23 in Saskatchewan, and 15 in Manitoba. Each province will collect a

Eligible TB Cases to May 31, 2008

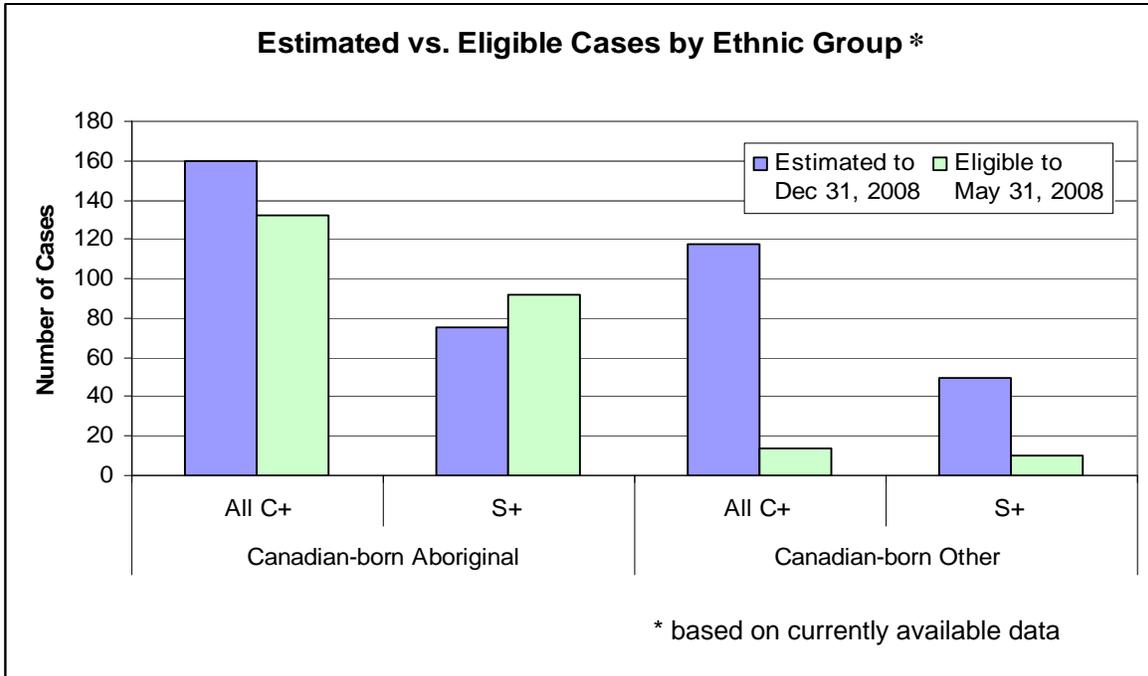


maximum of 25 in-depth interviews for qualitative analysis. The breakdown of eligible cases by province is graphically represented on the top left, and the graph below indicates the total number of estimated cases (based on historical data) compared to the actual number of eligible cases to date and the total number of cases that have undergone the structured and in-depth interviews to date. According to these numbers, the estimate for culture positive cases is in line with the current number of eligible cases, while the number of smear positive cases, indicating a higher degree of infectiousness, is expected to surpass the year-end projections.

Estimated, Actual, and Recruited DTT Case Numbers

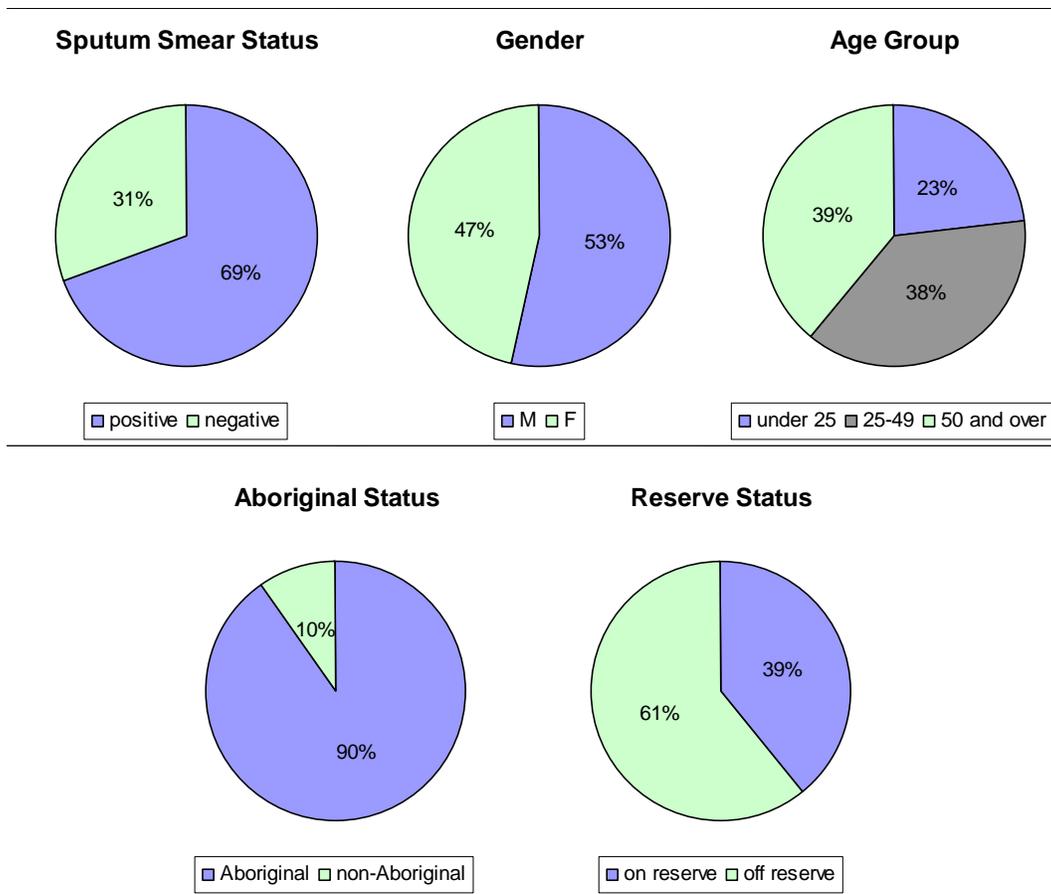


Although the number of eligible cases is consistent with estimates, the figure on page 11 shows that, of currently available data, the number of Canadian-born Aboriginal cases (especially smear positive cases) are higher than anticipated, and Canadian-born Other cases are much lower.



Descriptive Statistics

Based on available data on eligible cases from all three provinces, the following reports upon the descriptive statistics for data collected to May 31, 2008:



Qualitative Data

Qualitative data coding meetings were held in June and October of 2007 and January 2008. The meetings helped to identify themes that developed from the coding of qualitative interview data and to determine further lines of inquiry. These meetings also served as an opportunity for coordinators to share their diverse skills and experiences and seek guidance on interview and analysis techniques from the qualitative experts.



Coding meeting in Winnipeg, MB, October 2007



A display of a mapping exercise to help identify themes from existing codes

Preliminary findings:

In addition to themes identified in the development of the interview guide, study coordinators have noted the following:

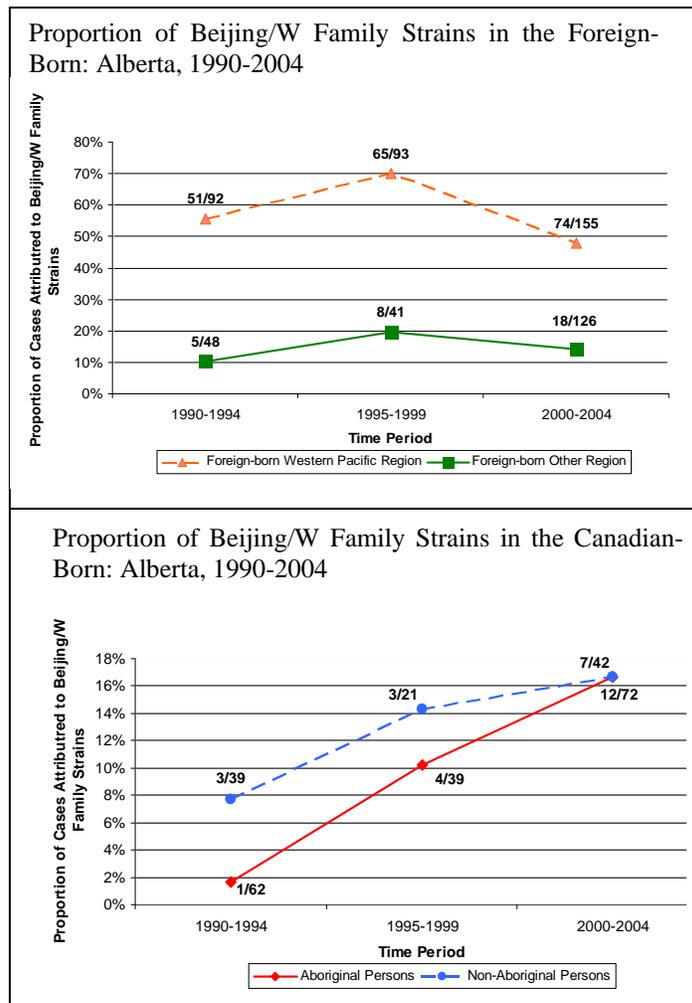
- i. Many patients fear their TB symptoms are indicative of cancer, which may have delayed health care seeking due to fear of related prognosis.
- ii. Many patients have noted the loss of loved ones, both friends and family, at young ages. This may be linked to a delay in health care seeking because of a general acceptance of death, or it may accelerate the progression to TB disease because of depression and its related health effects.
- iii. In Manitoba, the study coordinator noted that first symptoms reported by participants are not necessarily typical of what healthcare workers will look for when diagnosing TB.
- iv. The majority of participants in Alberta and Manitoba are interviewed while in isolation at the hospital. These participants often answer questions related to health, sickness, and the negative side of TB with reference to hospital stays, whereas participants in Saskatchewan, who are typically interviewed in their communities where they are treated by DOT workers, are often preoccupied with lack of confidentiality in TB treatment.

These themes, along with Network Committee discussions, helped to inform an updated version of the interview guide that was implemented in the study in late 2007.

Laboratory Data

Genotyping by Mycobacterial Interspersed Repetitive Units (MIRU) is ongoing for all Saskatchewan and Manitoba case isolates. A Memorandum of Understanding was signed in 2007 between the Principal Investigator, the Alberta Provincial Laboratory for Public Health in Edmonton, AB, and the National Reference Centre for Mycobacteriology in Winnipeg, MB regarding the transfer of case isolates from Alberta to undergo typing by MIRU at the National Centre. The first year's case isolates have been completed. A similar agreement is underway for the transfer of all clustered Saskatchewan and Manitoba isolates (cases with the dominant type strain will be handled separately) to undergo typing by Restriction Fragment-Length Polymorphism (RFLP) in Alberta. Alberta isolates are routinely genotyped by RFLP.

Beijing/W typing is also wrapping up for all archived culture positive Alberta isolates from 1990-2006. To date 87% of isolates have been typed. Preliminary data from late 2007 indicated a significantly higher proportion of Beijing/W cases amongst foreign-born than Canadian-born persons, and a small, but not significant difference in the presence of Beijing/W strains among Canadian-born Aboriginal (9.8%) and Canadian-born non-Aboriginal (12.7%) persons (see figures below). The direction of this trend will be determined when the cases from later years have been added to the analysis. Sub-typing to determine virulence properties within the family of Beijing/W strains is projected to occur in 2008-09.



Upcoming Plans

The second year of the DTT project met expectations thanks to the hard work of the research team and the guidance of the Provincial Network Committees and collaborators. Year three of the DTT project promises similar levels of achievement, with a focus on data analysis for all aspects under study.

Plans for the immediate future include the roll out of the newly developed database system, a group retreat, and a show of appreciation to the participants in the project. For the database roll out, the data manager will make site visits in the summer of 2008 to troubleshoot and train study coordinators on the new system. In September a group retreat is planned for research staff in recognition of the upcoming analysis and dissemination phases of the project. The intent of the retreat is for the research staff to maintain balance in work and ensure continued positive relationships. Elders will lead the retreat with a Sweat lodge Ceremony in order to offer the cultural supports necessary for the inclusion of the Aboriginal participants' and Aboriginal researchers' reality within the research process. A coding meeting will coincide with the retreat in September, Network Committees will convene again in the fall, and a face to face co-investigator meeting is anticipated in the New Year. With the conclusion of data collection at the end of December 2008, thank you cards will be sent to all patients who so generously shared the experiences and stories with the project team.

Longer term goals include the further development of data dissemination and knowledge translation plans with communities across the prairies. There also remains interest in developing a Prairie-wide lay organization for the control of TB among the Aboriginal population and in developing a set of knowledge sharing workshops with Indigenous peoples in New Zealand along with collaborators at the University of Auckland. We also anticipate the involvement of additional trainees down the road.



Saskatchewan TB physician Dr. Jim Fenton (left) with the pilot on an early morning flight to a remote community.



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